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Arterial Remodeling in the Left Coronary System

The Role of High-Density Lipoprotein Cholesterol

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OBJECTIVES We sought to evaluate the plaque and patient variables related to arterial remodeling responses of early, de novo atherosclerotic lesions involving the left coronary artery.

BACKGROUND Coronary artery remodeling is a lesion-specific process involving either enlargement or shrinkage of atherosclerotic coronary arteries. There are little histologic data available correlating plaque morphologic and patient clinical characteristics with the degree and type of arterial remodeling in early atherosclerosis.

METHODS We studied 736 serial arterial sections from the left coronary system of 97 autopsy cases (mean age 33 ± 11 years) by correlating the arterial remodeling response to plaque with demographic, serologic and histologic variables. Using the most proximal section as a reference, and considering the expected degree of internal elastic lamina tapering, remodeling was classified as positive (including neutral remodeling or compensatory enlargement) or negative.

RESULTS Remodeling was classified as positive in 84.3% (compensatory in 30.6%) and negative in 15.7% of sections with an overall mean luminal stenosis of 10.4 ± 9.9%. In the lesions with the greatest arterial cross-sectional narrowing from each case, compensatory enlargement was associated with higher high-density lipoprotein (HDL) cholesterol (59.4 ± 27.2 mg/dl) compared with either neutral (49.3 ± 15.5 mg/dl) or negative remodeling (30.4 ± 5.2 mg/dl; $p = 0.019$). In subjects with advanced atherosclerosis (maximum American Heart Association histologic grade 5 atherosclerosis), there was a modest linear relationship between higher HDL cholesterol and the propensity for positive remodeling ($r^2 = 0.37$; $p = 0.025$). On multivariate analysis, only HDL cholesterol was related to the arterial remodeling response.

CONCLUSIONS Negative arterial remodeling occurs in early atherosclerosis. Higher HDL cholesterol may favor positive remodeling. (J Am Coll Cardiol 1999;34:760–7) © 1999 by the American College of Cardiology

Arterial remodeling in response to atherosclerotic plaque has been described as an early adaptive process of arterial cross-sectional area (CSA) enlargement that acts to "accommodate" the enlarging plaque. The original description by Glagov et al. (1) identified coronary arterial remodeling as compensatory arterial enlargement. Their data demonstrated luminal dimensions to be preserved via arterial expansion for a histologic stenosis of up to 30% to 50%, with increases in plaque size beyond this threshold resulting in a progressive loss of luminal area. Thus, compensatory ("positive") arterial remodeling acts to limit the effect of the atherosclerotic plaque on luminal narrowing. Others have subsequently confirmed compensatory enlargement (2–10), although the magnitude of compensation is controversial (11,12). More recent studies have extended these early observations by describing so-called "paradoxical" or "negative" arterial remodeling defined as the shrinkage of the internal elastic lamina (IEL) in response to the enlarging atherosclerotic plaque (7,12–14). These studies show that negative remodeling is less common than positive remodeling.

The mechanism of arterial remodeling is uncertain because of the difficulty in longitudinally studying coronary arteries over the lengthy time interval over which remodeling likely occurs, and because of limited data from relevant animal models (10). Postulated mechanisms include effects of plaque size and shear stress (15–18) and the effects of specific plaque characteristics including plaque eccentricity (19,20) or fibrocalcific elements (13,14). Other proposed mechanisms include the degradation of connective tissue elements of the vessel wall by inflammatory mediators (21,22) or effects mediated through a functionally deficient vascular endothelium (15). In this study, we have investi-

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Abbreviations and Acronyms

AHA = American Heart Association
ANOVA = analysis of variance
CSA = cross-sectional area
EEL = external elastic lamina
HDL = high-density lipoprotein
IEL = internal elastic lamina
LAD = left anterior descending coronary artery
LCX = left circumflex coronary artery

gated the relationships of the plaque and vessel wall interaction through a detailed examination of the morphology of coronary arterial plaques. Specifically, we investigated the relationships between plaque variables (such as plaque size and morphologic characteristics), patient factors (including those associated with endothelial dysfunction, such as tobacco use, hyperlipidemia and diabetes mellitus) and the different arterial remodeling responses to atherosclerosis.

METHODS

We examined hearts from 97 subjects between the ages of 16 and 70 years who were consecutively referred to the Armed Forces Institute of Pathology through an autopsy consultation service provided to the Office of the Chief Medical Examiner of the State of Maryland (Baltimore, Maryland) between the years 1992 and 1994. Demographic measures included age, gender, race, height, weight, cause of death and heart weight (23). Body surface area (m^2) was calculated using the formula: (height [cm] × weight [kg])/ $3{,}600)^{1/2}$ (24). Postmortem serologic measurements, as previously described (23), included albumin, total and high-density lipoprotien (HDL) cholesterol and thiocyanate level. Red blood cells were analyzed for glycosylated hemoglobin as a marker for diabetes mellitus (25). All cases were screened for postmortem serum quality using serum albumin (26). Cases with a serum albumin below 2.5mg/dl (the lower limit of normal for the reference laboratory) were considered to have degradation of serum and were therefore excluded from this study. Serum thiocyanate indicated tobacco use when the serum level was ≥90 mol/L (23).

The hearts were weighed and perfusion fixed via the aortic stump at 100 mm Hg with 10% buffered formaldehyde for 30 min to distend the coronary arteries to physiologic pressure. Sections for histology were cut perpendicular to the long axis of the artery from serial locations approximately every 10 mm in the left anterior descending (LAD; five sections per artery) and left circumflex (LCX; three sections per artery) coronary arteries. Tissues were dehydrated in a graded series of alcohols and embedded in paraffin. Sections were cut (4 to 5 μm thick) and stained with hematoxylin and eosin and Movat pentachrome.

Morphometry was performed by computerized planimetry (version 2.5; IP Lab Spectrum, Vienna, VA). Movat pentachrome-stained arterial sections were magnified and digitized, and the luminal, IEL and external elastic lamina (EEL) perimeters were measured. Sections (n = 25) taken at a side branch location or that were considered to be distorted from processing artifact were excluded, thus leaving 736 sections for further analysis. Arterial areas were calculated from the diameter values derived from the measured arterial perimeter (area = πr^2) to avoid artifacts encountered from distortion of arterial shape during processing. Plaque was defined as the area enclosed between the IEL and the lumen. Plaque area was calculated as the difference between IEL and luminal area measurements. Percentage luminal stenosis was calculated as the plaque area/IEL area × 100 (1). This calculation represents the pathologically defined luminal stenosis, and may not reflect an actual decrease in lumen area (e.g., as defined on coronary angiography).

Histologic sections were graded on light microscopy according to the classification scheme of the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association (AHA grade) (27,28). Lesions were further histologically characterized according to their associated degree of eccentricity. Concentric plaques were those plaques with a plaque thickness greater than medial thickness along the entire circumference of the vessel. Otherwise, the plaque was classified as eccentric. The degree of eccentricity was defined as the percentage of the IEL circumference occupied by the eccentric plaque. Inflammatory cells were identified as present or absent, and graded as follows: 0 (absent), 1 (minimal inflammatory cells), 2 (single collection of inflammatory cells in a discrete location), 3 (multiple foci of inflammatory cell infiltrates) and 4 (extensive inflammatory cell infiltrates throughout the arterial wall). Calcium was graded as present or absent, and semiquantitated on a scale of 0 to 4 according to the number of quadrants containing calcium on the arterial cross section. For comparison of cases, histologic characteristics were considered as present in any section, or absent.

Classification of arterial remodeling. Arterial sections were classified as demonstrating either positive or negative remodeling (Fig. 1). For each artery (LAD and LCX), the most proximal section was used as the initial reference for arterial size. The mean percent area stenosis in these reference sections was 11.2 ± 8.0%. For classification of the type of remodeling present in the more distal sections, the IEL area of each section was compared with the IEL area of the reference section and to the expected amount of "normal" arterial tapering. Arterial tapering was determined by measurement of IEL areas in a subset of 10 cases selected on the basis of having only minimal intimal thickening (total intimal CSA <1 mm^2). The normal vessel tapering between serial sections (approximately 10 mm between sections) was 1.20 ± 2.40 mm^2/cm for the LAD and 1.20 ± 2.15 mm^2/cm for the LCX. Abnormal tapering between adjacent sections was defined as tapering greater than the mean + 2 SD of the expected tapering. Based upon IEL areas in this study, abnormal tapering was present when a 25% or greater decrease in IEL

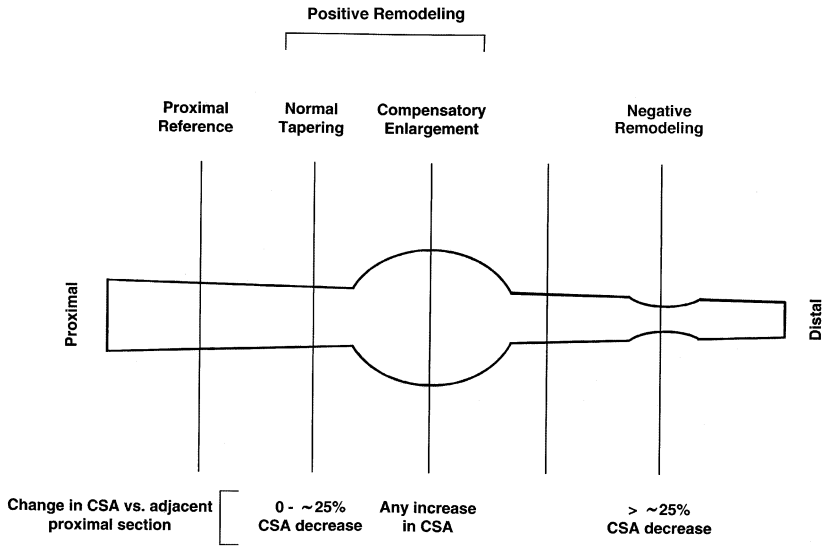

Figure 1. Schematic representation of the methods used to classify different types of arterial remodeling. Definitions as described in "Methods."

area was present between sections. This is comparable with data on arterial tapering determined by intravascular ultrasound, as reported by Mintz et al. (14,29).

Positive remodeling was defined as an increase in IEL area in successive sections (compensatory enlargement), or vessel tapering within the expected range defined as normal (neutral remodeling). Negative remodeling was identified as a decrement in IEL area, relative to the adjacent proximal sections, that was greater than the anticipated change with normal vessel tapering (Fig. 1). Two separate methods were used to classify the overall remodeling characteristics of individual cases. In the first method, cases were classified as overall demonstrating positive or negative remodeling. A case with all sections demonstrating positive remodeling was considered to have overall positive remodeling (n = 42), whereas a case with any single section demonstrating negative remodeling was classified as a "negative remodeler" (n = 55). In the second method, a mean remodeling score was calculated for each case by averaging assigned values of either 1 (positive remodeling), 2 (neutral remodeling) or 3 (negative remodeling) from each section.

Statistical analysis. The arterial remodeling response to atherosclerotic plaque was correlated with the serologic and histologic variables using the patient as the unit of analysis. Continuous variables were tested using a *t* test for the means of independent samples. Categorical variables were tested with a chi-square test or factorial analysis of variance (ANOVA). Univariate analyses were used to identify patient or histologic predictors of the arterial remodeling response. Multivariate linear regression analysis was used to explore the relationship between the arterial remodeling response and the variables HDL cholesterol and plaque area. For all statistical tests, a two-tailed p value of ≤ 0.05 was considered significant.

RESULTS

Study cases. The characteristics of the 97 study cases are displayed in Table 1. Mean age was 33.0 ± 11.2 years.

Table 1. Characteristics of Study Cases

Characteristic	Mean ± SD	Range
Number	97	
Age, yrs	33 ± 11	16–74
Race	55 Black, 42 White	
Heart weight, g	415 ± 71	247–690
Body surface area, m^2	2.0 ± 0.2	1.5–2.7
Total cholesterol, mg/dL	209 ± 61	93–372
HDL cholesterol, mg/dL	53 ± 22	22–138
Glycosylated hemoglobin, %	6.2 ± 1.7	2.9–20.2
Tobacco use, n, %	47 (48.5)	
Plaque size, mm^2	1.7 ± 1.9	0.0–11.39
IEL area, mm^2	14.6 ± 6.3	1.3–41.0
Luminal stenosis, %	10.4 ± 9.9	0.0–58.0

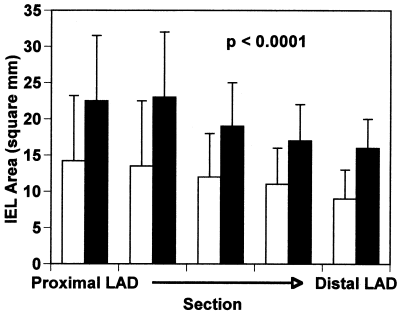

Figure 2. Mean IEL area (mm^2) for sections with plaque area <1 mm^2 **(open bars)** and ≥ 1 mm^2 **(black bars)** for serial LAD sections, proximal to distal (ANOVA $p < 0.0001$). At all sites, IEL area was smaller in sections with minimal plaque.

Serum thiocyanate levels indicated recent tobacco use in 47 cases. From the original group of 736 evaluated arterial sections, the most proximal section of both the LAD and LCX (194 sections) was used as a size reference. In the remaining 542 arterial sections, the mean IEL CSA was 14.6 ± 6.3 mm^2, and the mean plaque CSA was 1.7 ± 1.9 mm^2. Histologic characteristics of the study group included lesion eccentricity in 162 sections (29.9%), calcium in 69 (12.7%; grade 1, 6.5%; grade 2, 3.7%; grade 3, 2.6%; grade 4, 0%) and inflammation in 116 (21.4%; grade 1, 14.9%; grade 2, 4.6%; grade 3, 1.8%; grade 4, 0%).

Remodeling was classified in the 542 arterial segments as positive in 457 (84.3%) and negative in 85 (15.7%) sections. Sections with plaque area ≥ 1 mm^2 had larger IEL areas than sections with plaque area <1 mm^2 (Fig. 2). The mean IEL, plaque (Fig. 3), and luminal CSA were significantly larger in sections with positive versus those with negative remodeling. Negative remodeling was more common (22.2%) and compensatory enlargement was less common (16.5%) in sections with minimal plaque (<1 mm^2) than in sections with larger plaque area (>1 mm^2) (negative remodeling 9.6%, compensatory enlargement 43.8%; $p < 0.0001$).

Classification of the remodeling characteristics of each case included "positive" remodeling in 42 cases, and negative remodeling (based on the presence of at least one section with negative remodeling) in 55 cases. The univariate comparisons of demographic, serologic and histologic variables for the cases classified as positive and negative remodeling are shown in Table 2. Total serum cholesterol was significantly higher in cases classified as "positive" remodeling.

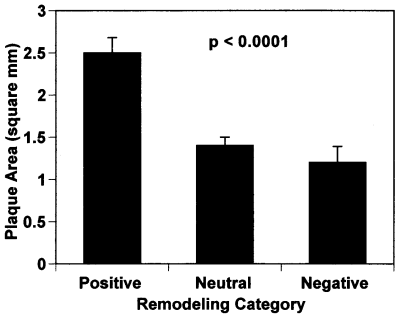

Figure 3. Mean plaque area (mm^2) for sections with compensatory, neutral and negative remodeling (ANOVA $p < 0.0001$) (mean ± standard error).

Remodeling and HDL cholesterol. The single lesions from each case with the greatest CSA narrowing (percent luminal stenosis) were evaluated to investigate the relationship between cholesterol and remodeling. Cases were included in this analysis when the lesion with the greatest percent luminal stenosis was not the most proximal reference segment. In this analysis, HDL cholesterol was significantly higher for cases with compensatory enlargement (59.4 ± 27.2 mg/dl) versus those sections demonstrating neutral (49.3 ± 15.5 mg/dl) or negative remodeling (30.4 ± 5.2 mg/dl) (ANOVA $p = 0.019$) (Fig. 4). Total cholesterol tended to be higher in the groups with compensatory and neutral remodeling, although these differences were not significant. The ratio of total and HDL cholesterol tended to be increased in the group with negative remodeling (6.3 ± 2.7) compared with either compensatory (4.5 ± 2.1; $p = 0.08$) or neutral remodeling (4.5 ± 1.8; $p = 0.07$). There were no significant univariate relationships between the remodeling characteristics of these lesions and all histologic variables, including plaque calcification, inflammation, eccentricity or atherosclerosis grade. The frequency of smoking did not differ ($p = 0.38$) among lesions with compensatory (8/20, 40%), neutral (15/26, 58%) or negative (2/5, 40%) remodeling. Multivariate analysis including the variables HDL cholesterol and plaque area showed a significant relationship between HDL cholesterol and positive remodeling ($p = 0.006$).

To confirm these results in the most severe lesions on a percent luminal stenosis basis, further subgroup analysis was performed on cases having at least one section with advanced atherosclerosis (AHA grade 5; $n = 13$ cases; $n = 72$ sections) to analyze the associations of demographic and serologic variables with arterial remodeling. In this analysis, the mean HDL cholesterol level was significantly higher for cases with positive remodeling (68.4 ± 27.9 mg/dl) versus those with negative remodeling (35.9 ± 14.9 mg/dl; $p = 0.018$). There was a significant linear relationship between HDL cholesterol and the calculated average remodeling score for these cases. Higher HDL cholesterol was associated with an overall propensity for positive remodeling ($r^2 = 0.37$; $p = 0.025$) (Fig. 5).

DISCUSSION

Recent studies on arterial remodeling in atherosclerosis have indicated that arterial remodeling is a heterogeneous process including both positive and negative remodeling (7,13,14). The clinical importance of these divergent arterial responses to atherosclerotic plaque is readily apparent. Whereas arterial enlargement may delay the onset of obstructive conse-

Table 2. Demographic and Serologic Characteristics of Subjects with Positive or Negative Arterial Remodeling

Characteristic	Remodeling Category		p
	Positive	Negative	
Cases	n = 42	n = 55	
Age	32.3 ± 9.4	34.2 ± 12.1	0.39
Body surface area, m^2	1.97 ± 0.27	1.97 ± 0.21	0.94
Heart weight, g	391 ± 66	400 ± 87	0.58
Tobacco use, n, %	20 (47.6)	27 (49.1)	0.89
Glycosylated hemoglobin, %	6.3 ± 0.9	6.1 ± 2.1	0.66
Total cholesterol, mg/dL	223.9 ± 64.3	196.7 ± 56.6	0.03
HDL cholesterol, mg/dL	55.3 ± 21.1	52.1 ± 22.9	0.50
Mean plaque area (mm^2/section)	1.54 ± 1.24	1.59 ± 1.08	0.83
Plaque calcification, n, %	11 (35.5)	19 (34.5)	0.38
Plaque inflammation, n, %	18 (42.9)	26 (47.3)	0.67
Plaque eccentricity, n, %	17 (40.5)	16 (29.1)	0.21

quences of atherosclerosis, arterial narrowing may accelerate the development of symptomatic atherosclerosis by contributing to the luminal reduction created by the plaque (7,14). An important example of the impact of negative remodeling is found in postangioplasty restenosis where a significant proportion of the late loss in luminal area may occur because of vessel shrinkage rather than plaque growth (30,31). Thus, the interaction between an atherosclerotic plaque and the arterial wall, and the factors, particularly modifiable coronary risk factors, that may modulate this process have important consequences for patients with atherosclerosis.

Mechanisms of arterial remodeling. Several hypotheses on the mechanism of arterial remodeling have been proposed. One hypothesis relates arterial remodeling to plaque size, with arterial enlargement resulting from flow-mediated changes in shear stress created by the enlarging atherosclerotic plaque (9,16–18). This hypothesis arose from early observations on compensatory arterial enlargement and provided the initial evidence relating arterial size to the size of the underlying plaque (1,2). However, these data, derived from pooled analysis of study subjects, have subsequently been questioned because normal interpatient differences in arterial size might heavily influence this relationship (11). These data also provide no insights into the mechanism of negative remodeling that has been associated with smaller arterial plaques (14). Recent data provide a potential explanation for this seeming paradox, as negative remodeling has been associated with the presence of fibrocalcific atherosclerotic elements (13,14) that may impair the capacity of an arterial segment to enlarge.

Other hypotheses on the mechanism of arterial remodeling have been proposed. A functionally intact endothelial surface may modulate arterial remodeling (15). This hypothesis has been indirectly derived through associations of negative remodeling in de novo and restenotic lesions with coronary risk factors that impair vascular endothelial cell function, including tobacco use (13), hyperlipidemia (13) and diabetes mellitus (31). The endothelium can theoreti-

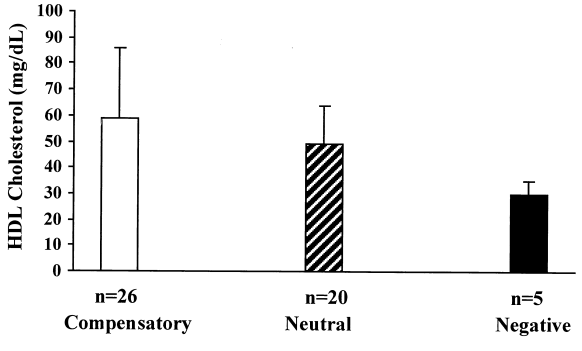

Figure 4. Mean HDL cholesterol values associated with different types of arterial remodeling including compensatory **(open bar)**, neutral **(hatched bar)** and negative **(black bar)** subtypes (ANOVA p = 0.019) (mean ± standard deviation).

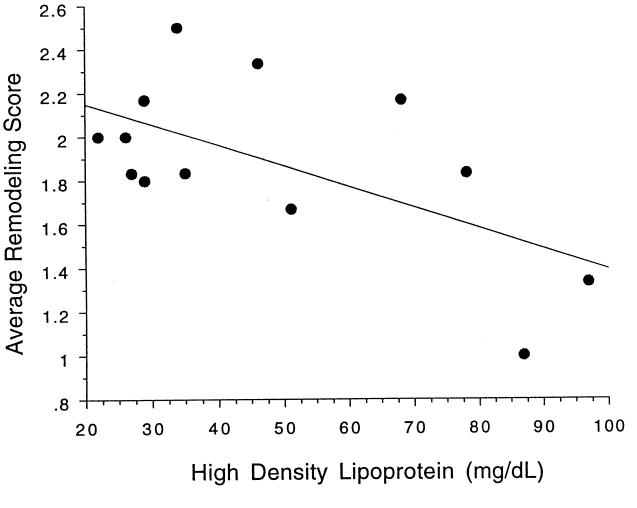

Figure 5. Relationship between the remodeling score and HDL cholesterol for cases with advanced (AHA grade 5) atherosclerosis. A higher remodeling score indicates a greater frequency of sections displaying negative remodeling (r^2 = 0.37; p = 0.025).

cally sense changes in shear stress or humoral factors, transduce these signals to adjacent cells and release substances that may participate in the remodeling process (15). Within this paradigm, an endothelial lining that is physically or functionally deficient could impair the production of locally acting vasodilating substances, such as nitric oxide, and impede arterial remodeling. Lastly, inflammatory mediators, such as matrix metalloproteinases derived from macrophages contained within the atherosclerotic plaque (32), may degrade fibrous elements in the vessel wall leading to vessel enlargement (21,22).

Each of these hypotheses on the mechanism of arterial remodeling has been primarily derived from advanced atherosclerosis, with many of the most recent observations on arterial remodeling made in symptomatic patients undergoing coronary revascularization. Thus, these data may be biased for features seen predominantly in advanced atheroma, such as calcification, and be less applicable to the broader range of atherosclerotic lesions.

The Present Study

Our data, from de novo and predominantly early atherosclerosis, provide further insights into the associations and possible mechanisms of arterial remodeling.

The role of HDL in remodeling. We found a significant relationship between higher HDL cholesterol and positive remodeling in advanced atherosclerosis. Low HDL cholesterol is an established risk factor for the development of coronary artery disease, whereas medications that increase HDL cholesterol reduce myocardial ischemia and the need for coronary revascularization (33–35). Our data suggest that HDL-mediated arterial wall remodeling, in addition to remodeling of the atherosclerotic plaque by reverse cholesterol transport (36), may account for the results of atherosclerotic regression trials. Ongoing studies using intravascular ultrasound for the evaluation of atherosclerotic regression should provide further insights into this issue.

Negative remodeling and previous studies. This is the first study to demonstrate that negative remodeling, previously described in advanced, symptomatic atherosclerosis, occurs in early atherosclerosis. Two factors previously associated with negative remodeling are tobacco exposure and arterial calcification. Fibrocalcific plaque elements and superficial calcium, as defined by intravascular ultrasound, have been associated with negative arterial remodeling (14). This possible relationship has conceptual appeal, considering that a noncompliant, calcified arterial wall may be incapable of enlarging to accommodate an enlarging plaque due to specific biomechanical characteristics (37). However, the high frequency and diffuse nature of calcified elements in advanced atherosclerosis undergoing revascularization (38,39) raise the question of the importance of the association between negative remodeling and fibrocalcific plaques. In our study of predominantly early atherosclerosis, calcified elements were less prevalent than these studies, yet the prevalence of negative remodeling was similar. We found that calcification was not an independent predictor of arterial remodeling, an observation that is consistent with the findings of others (10). Also, in contrast to a previous study (13), we found that tobacco use was unrelated to negative arterial remodeling. Given these contradictory data from different patient populations, the associations of vascular calcification and tobacco use with negative arterial remodeling remain speculative.

Study limitations. Autopsy studies are limited by perturbation of the tissue at the time of pathologic examination, and vessel distortion from fixation and sectioning. However, our methods including pressure fixation of the coronary arteries via the aortic stump and geometric correction of the IEL area based on the measured IEL perimeter should minimize the effect of processing artifacts. Intravascular ultrasound has the advantage of identifying the least diseased proximal arterial segment before side branches for determination of an appropriate reference site. Intervening arterial side branches possibly affect the measurement of arterial areas, but this has been included in calculations of normal vessel tapering. Despite the potential effect of these side branches, the anticipated amount of arterial tapering was comparable with that defined by Mintz et al. with intravascular ultrasound (29). Conversely, direct measurement of arterial areas via pathologic morphometry avoids errors arising in approximating the arterial borders in fibrocalcific plaques during ultrasound measurements (40).

Autopsy tissues provide an important means of evaluating a large number of arterial segments in comparison with a reference segment, but do not allow for the serial evaluation of plaque morphology across time. The ubiquitous presence of atherosclerosis, even in patients with angiographically normal coronary vessels, creates uncertainty in the definition of a particular segment as a size reference (41). Thus, in our study, as in any study of arterial remodeling, the reference segments may have undergone positive or negative remodeling and created error in the categorization of remodeling in the distal segments. Despite this concern, the IEL CSA was greatest in sections demonstrating positive remodeling, and least in sections demonstrating negative remodeling, as anticipated based on the current paradigm of arterial remodeling. An effect of reference segment atherosclerosis is likely minor in the present study because of the minimal CSA narrowing present in the proximal reference segments compared with previous studies with reference segments that have contained up to 30% to 50% CSA narrowing (7,14). Our data on HDL cholesterol and remodeling are derived from selected subgroups of patients, and thus should be cautiously interpreted and require replication in future studies. Lastly, differences in exposure duration could account for the absence of a relationship between tobacco use (13) and negative remodeling in our study.

CONCLUSIONS

Arterial remodeling occurs in both early and in advanced atherosclerosis. Negative arterial remodeling occurs even with small accumulations of atherosclerotic plaque. In more severe atherosclerosis, higher HDL cholesterol may favor positive remodeling and thereby contribute to the beneficial clinical effects of cholesterol-modifying pharmacologic agents.

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